ORIGINAL ARTICLES

EXPERIMENTAL YELLOW FEVER.

BY

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Subsequent to the presentation of our paper to the Pan-American Congress[1] in Havana, we succeeded in producing some additional cases of yellow fever at our Experimental Sanitary Station near Quemados, Cuba. We have thought that brief reports of these cases, to be followed by remarks on experimental yellow fever from the clinical point of view, would be of interest to the members of this Association, and especially to those who reside in sections of the country where each year yellow fever is liable to appear in epidemic form.

Perhaps it might be well to recall the fact that the cases of yellow fever here to be recorded were produced like those heretofore reported by us, under strict quarantine regulations and at a special Experimental Sanitary Station, near the town of Quemados, Cuba.

In the series of 12 experimental cases produced at this camp during the period from December 5, 1900, to February 7, 1901—an interval of 65 days—it should be borne in mind that the order of occurrence exactly corresponded with the order of inoculation, except that Case II, inoculated at 4 p.m., December 8, 1900—having a longer period of incubation than Case III, inoculated at 10.30 a.m., December 9, 1900—the order of their relative occurrence became reversed[2]. Moreover the attack always followed within the period of incubation of the disease, and concerned only those nonimmune individuals who had consented to submit themselves for experimentation. Of a total of 16 individuals who thus consented, 14 contracted yellow fever; whereas of 5 nonimmunes, who did not consent and were therefore not subjected to experimentation, none acquired the disease, although otherwise placed under exactly similar surroundings. In its occurrence, therefore, at this station, yellow fever strictly obeyed the behests of the experimenters, both as to place and time of occurrence. Recovery took place in all cases.

(A) CASES PRODUCED BY THE INJECTION OF BLOOD.

CASE I.—W. J., American, nonimmune, aged 27—in quarantine since December 20, 1900—with his full consent, at 11 a.m., January 4, 1901, was injected subcutaneously with 2 cc. of blood taken from the general circulation of a case of mild yellow fever at the beginning of the second day of the disease and having a temperature of 100.8°F. The subject, who had been in strict quarantine at the station for the period of 45 days, remained in his usual health until the early morning of January 8, when he complained of slight frontal headache. At 6 a.m. his temperature was 98.2°F. and pulse 70; 9 a.m., temperature 99.8°F., pulse 95; frontal headache increased, with slight, chilly sensations in the feet and lower extremities. There was some congestion of the eyes and his usual florid complexion was heightened in color. At 10.15 a.m., temperature 100.6° F. pulse 97. Complains of some pain in the lumbar region. At 11.20 a.m., temperature 101.4°F., pulse 99. The height of the febrile paroxysm was reached at 3 p.m., the same day, when the temperature was 103.4°F. and pulse 108. The facial expression was now characteristic of yellow fever. The eyes were deeply injected and watery and the face much suffused. Photophobia moderate—frontal headache and backache severe. The skin was moist.

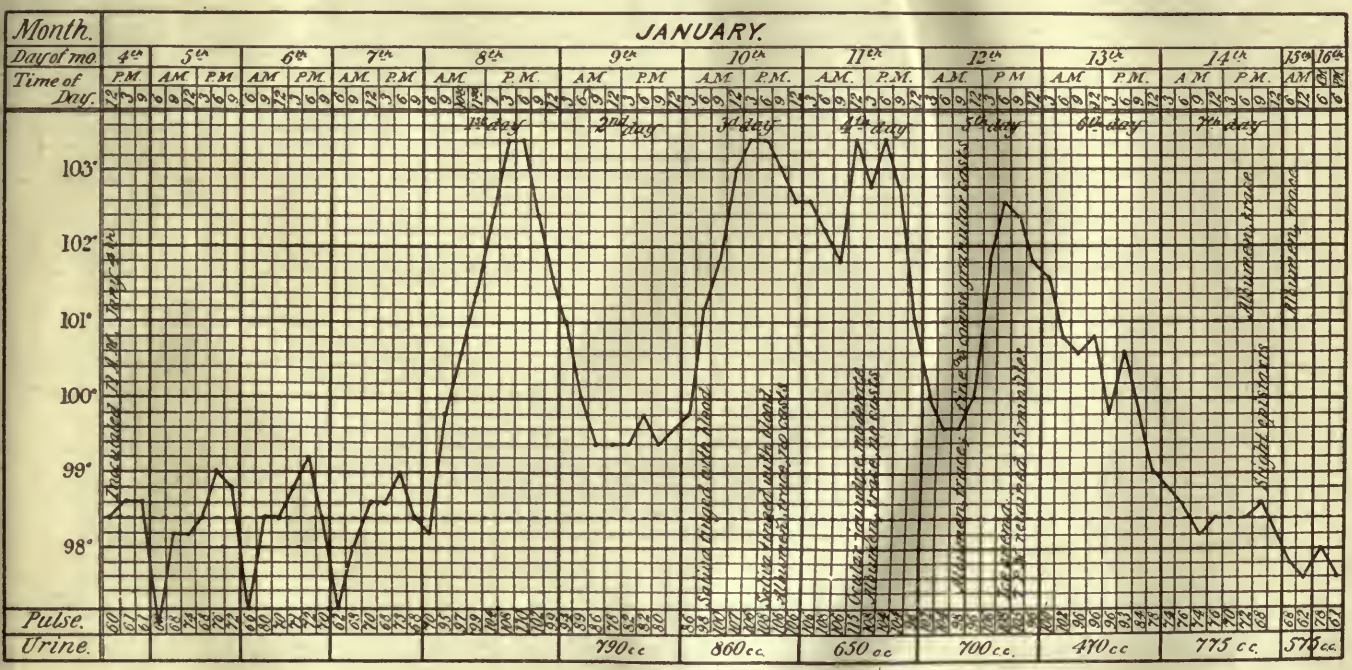

Chart I.—Yellow fever produced by injection of 2 cc. of blood. Period of incubation, 3 days, 22 hours.

The remission occurred at the end of 24 hours—9 a.m. January 9—when the temperature had fallen to 99.4°F. and the pulse to 86. The subsequent history was that of a case of yellow fever of moderate severity. Albumin was found in the urine at the end of the sixty-first hour. There was some bleeding from the gums on the third day and moderate ocular jaundice on the fourth day. Fever disappeared on the morning of the seventh day. (Chart I.)

CASE II.—W. O., American, nonimmune, aged 28, in quarantine since December 20, 1900. On January 8, 1901, at 9 p. m., with his full consent, he was given by subcutaneous injection 1.5 cc. of blood taken from the mediancephalic vein of Case I, just 12 hours after the beginning of the attack and when the temperature was 102.4° F.—that is, just after the first febrile paroxysm began to decline. The subject remained in his usual condition during the following 2 days.

January 11, 1901, at 6 a. m., his temperature was 98.9° F. and pulse 70. He complained of being disturbed by dreams during the night and had some frontal headache. At 9 a. m., temperature 100° F., pulse 77. At 10.15 a. m., temperature 101.4° F., pulse 76. Eyes decidedly congested and face moderately suffused. At 12 o'clock noon, when the temperature had risen to 103.2° F. and the pulse to 102, the height of the primary paroxysm had been reached. Headache and backache were now much complained of. The facial expression was characteristic. The remission occurred at the end of 24 hours, lasted one day and was followed by a very moderate secondary fever. A distinct trace of albumin was found in the urine passed at 2 a.

[1] The Etiology of Yellow Fever. An Additional Note. Read at the Pan-American Congress, Havana, February 4-7, 1901.
[2] These cases were reported in our Additional Note.

m. January 12, seventeen hours after the attack began. A few hyaline casts were also present. Slight bleeding from the gums occurred on the second and third days of sickness. The character of the attack in this case was very mild. The albumin, which at no time amounted to more than a distinct trace, did not disappear, however, until January 24. (Chart II.)

CASE III.—W. F., American, nonimmune, aged 23, was, with his full consent, at 1 p. m. o'clock January 22, 1901, injected subcutaneously with 0.5 cc. of blood taken on the second day from the general circulation of a severe case of yellow fever, which was fatal on the seventh day of the disease. The patient's temperature, when the blood was withdrawn, was 103° F. and pulse 90. The subject remained well during the following day. January 24, at 6 a. m., his temperature was 98.4° F. and pulse 78. He partook of a hearty breakfast at 6.30 a. m., which he vomited soon afterward. At 7 a. m. he complained of dizziness and general lassitude. Temperature, 98.4°, pulse 78. At 9 a. m., chilliness complained of, but there is no record of temperature or pulse. At 9.30 a. m., temperature 100.6° F., pulse 82. Frontal headache well marked. Eyes already injected and face slightly suffused. 10.30 a. m., temperature 101.2° F., pulse 86. An hour later his temperature was 102.6° F. and pulse 82. The height of the primary paroxysm was reached at 1 p. m., when the temperature was 102.8° F. and pulse 98. At this hour photophobia was well marked and constant complaint made of severe frontal headache and backache, together with pains in the lower extremities. The skin was moist. The remission occurred at the end of 36 hours. The subsequent course was that of a case of yellow fever of moderate severity. With the return of the secondary fever there were present sharp backache and headache. *Albumin* appeared in the urine at the end of 57½ hours. Ocular jaundice was present on the third day and thereafter until convalescence. The gums did not bleed, although they were swollen and injected. Fever subsided on the sixth day, and albumin disappeared on the eighth day. (Chart III.)

CASE IV.—J. H. A., American, nonimmune, aged 22, with his full consent, received subcutaneously, at 12.15 p. m., January 25, 1901, 1 cc. of blood taken from the mediancephalic vein of Case III, just 27½ hours after the commencement of the latter's attack of yellow fever (T. 100.6° F.). The subject remained in his usual condition during January 26 and 27, except that on the afternoon of the last mentioned date, he complained of occipital headache. This was present on the following morning, January 28; otherwise he felt well. His temperature at noon was 98.6° F., and pulse 68. Occipital headache continued. He partook of dinner with fair appetite. He was not seen again until 3 p. m. In the meanwhile, at 1.15 p. m., the subject states that, while sitting alone in his tent, he began to feel cold, and that this was quickly followed by a decided chill with increase of headache. He noted the hour in writing at the time. At 3 p. m. his temperature was 103.6° and pulse 120. The eyes were intensely congested and the face deeply suffused. The patient was very restless, and complained bitterly of occipital headache and backache. Photophobia was very marked. He vomited several times within the next 2 hours. Skin hot and dry. The height of the primary paroxysm was reached at 3.30 p. m., at which hour the temperature was 104.2° F., and pulse 120. The subsequent history was one of severe yellow fever. There was no remission in the fever until the fourth day, when the temperature fell to 101.2° F. Now, for the first time, the patient ceased to complain of occipital headache and backache. Albumin appeared at the end of 18¼ hours (7.30 a. m., January 29). A few hyaline casts were also present at this time. The specimen of urine passed at 6.40 a. m., January 30 contained albumin $\frac{1}{20}$ by volume, and many fine and coarse, granular, bile-tinted casts. Ocular jaundice appeared on the third day The skin of the face and of the anterior part of the neck and thorax was tinted on the fourth day. This rapidly became intensified and general. The secondary fever lasted about 30 hours, the temperature falling to 97.2° F. at 12 o'clock (midnight) of the fifth day. Marked fluctuations of temperature continued until the eleventh day of illness. Recovery was slow and much delayed by the development of a carbuncle in the left sacral region. A trace of albumin was still present on March 1, 32 days after the attack had begun. (Chart IV.)

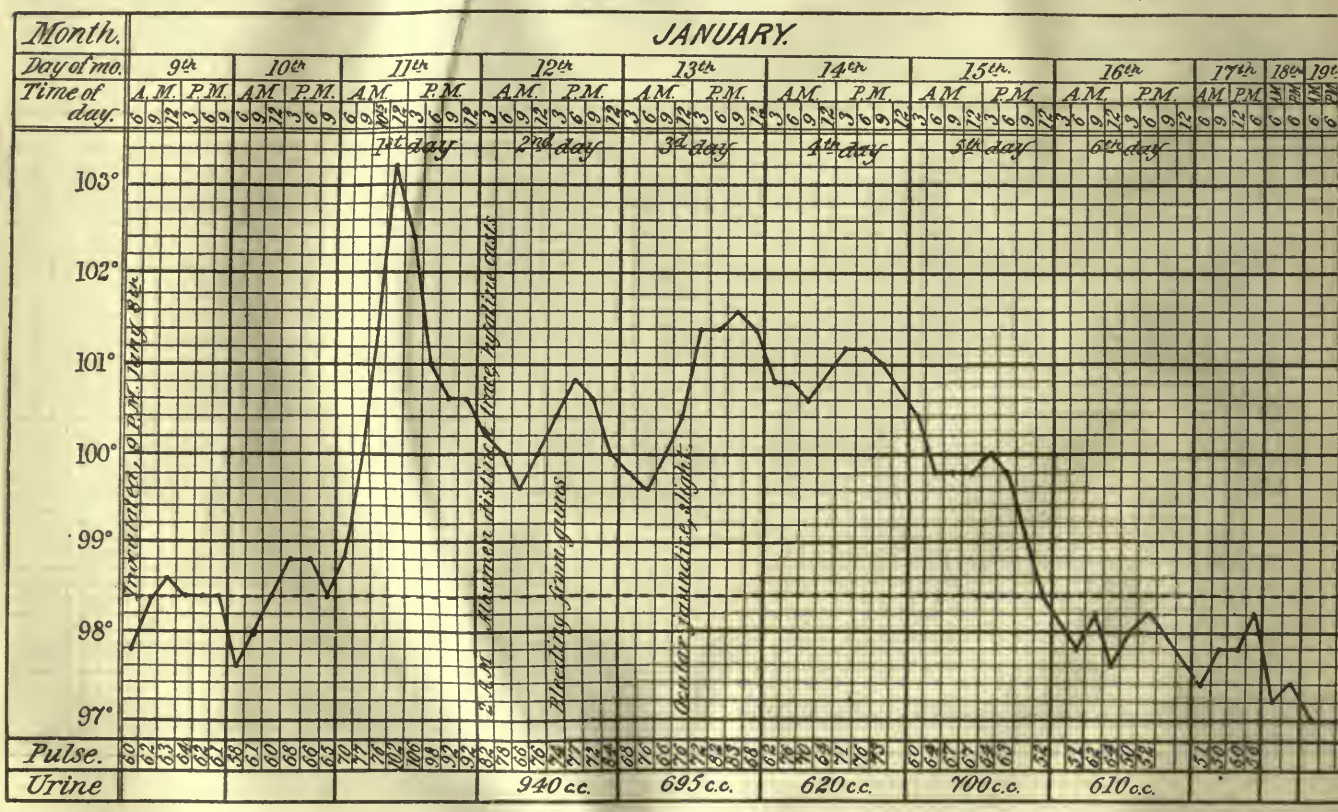

Chart II.—Yellow fever produced by injection of 1.5 cc. of blood. Period of incubation, 2 days, 12 hours.

The production of yellow fever by the injection of blood taken from the general circulation is of much interest as showing: first, that the parasite is present in the blood, at least during the early stages of the disease; and secondly, that its passage through an intermediate host, although this would seem to be nature's method, is not essential in the life cycle of this parasite. Thus yellow fever is analogous to the malarial fevers, in that it may be produced either by the bite of a certain species of mosquito, or by the injection of blood taken directly from the general circulation.

Another point to which we have elsewhere referred, but which is considered of sufficient importance to here bear repetition, is that in each of the foregoing cases of experimental yellow fever produced by the injection of blood, careful cultures made from the same blood drawn from the vein immediately after injection or, as in one instance, made from the same syringeful of blood that

conveyed the disease, failed to show the presence of Sanarelli's bacillus. In one case colonies of Staphylococcus pyogenes citreus were obtained, while in the remaining 3 cases, no growth whatever occurred. The exclusion of the Bacillus icteroides from further consideration as the specific agent of yellow fever would, therefore, seem to have been conclusively determined by these experiments.

(B) CASES PRODUCED BY THE BITE OF THE MOSQUITO, CULEX FASCIATUS.

CASE V.—L. F., American, nonimmune, aged 28—in quarantine since December 20, 1900—was, with his full consent, at 3.30 p. m., January 19, 1901, bitten by 3 mosquitos that had been contaminated 39 days previously, by feeding on the blood of a well-marked case of yellow fever, on the third day of the disease. The subject remained in his usual conditon of health until the afternoon of January 23. At noon of this date his temperature was 97.8°. Soon after this hour he took to his bed, complaining of frontal headache and general lassitude. At 3 p. m. his temperature was 99.2° and pulse 78. At 4.10 p. m. the temperature was 100° F. and the pulse 104. A sense of chilliness, especially of the lower extremities, and increased frontal headache, were now complained of. Eyes already injected and face flushed. At 5 p. m. the temperature was 101.2° F. and pulse 104. The height of the paroxysm was reached at 8.20 p.m., at which hour the temperature was 103.6° F. and the pulse 110. The eyes were deeply congested and photophobia very marked. Headache and backache were so intense as to cause the patient to complain bitterly. He vomited once at 9 p. m. January 24, 3 a. m., the temperature had fallen to 100.2° and the pulse to 104, but with only slight amelioration to the patient's discomforts. At noon the thermometer marked 102°. Remission occurred at the end of 33 hours, with marked diminution of all disagreeable symptoms. The secondary fever, attended by increased headache and backache, lasted 4 days, the temperature dropping to normal at 6 p. m. of the seventh day. The case was one of moderate severity. Albumin appeared in the urine at the end of the forty-second hour. Ocular jaundice was quite noticeable on the afternoon of the second day. Some jaundice of the face and anterior region of the chest was seen on the fourth day. Many bile-tinted granular casts were present in the urine on the third day, and thereafter until the eleventh day. The albumin which reached ¼ by volume on the sixth day disappeared on the twelfth day. (Chart V.)

CASE VI.—C. W., American, nonimmune, aged 27, with his full consent, was, at 9.30 a. m., January 31, 1901, bitten by 2 of the 3 mosquitoes that had been applied to the foregoing Case V. The interval that had elapsed since their contamination was, therefore, 51 days. The subject remained well until 12 o'clock noon, February 3, when he complained of heaviness in his legs and some supraorbital pain. His temperature at this hour was 99° F. and pulse 70. At 1.30 p. m. it had risen to 100° F., and at 5 p.m. to 100.6° F. and pulse to 84. The primary rise of fever, which was somewhat fluctuating in character, did not reach its height until at the end of 24 hours, noon, February 1, when the temperature was 102.4° and the pulse 92. The facies was now suggestive of yellow fever. Remission occurred at the end of 45 hours and lasted for about 1 day. The secondary rise was slight in character, the temperature falling to normal on the morning of the sixth day. The case was very mild in character. Albumin appeared at the end of 75 hours (beginning of fourth day); it never amounted to more than a distinct trace and disappeared on the eighth day. There was no ocular jaundice, and although the gums were injected and swollen, there was no hemorrhage at any time. The patient perspired freely throughout the attack. Convalescence was rapid. The subject had been in quarantine for the period of 6 days prior to inoculation. (Chart VI.)

CASE VII.—J. H., American, nonimmune, aged 26, with his full consent, was bitten at 11 a. m., February 6, 1901, by the same 2 mosquitos that had 6 days previously, bitten Case VI. Fifty-seven days had therefore elapsed since the insects had been contaminated by biting a case of yellow fever. He remained well until 12 o'clock noon, February 9, when he experienced slight chilly sensations, accompanied by yawning. At this hour his temperature was 99° F. and pulse 72. At 3 p. m., temperature 98 8°, pulse 72. Says that he feels "out of sorts," but has no headache. At 5.30 p. m. his temperature was 100.6° F., pulse, 78. He was not seen until 7.30 p. m., when he complained of backache and severe general headache, more intense through the frontal region. Eyes much injected, photophobia very marked, face flushed. He was stretching and yawning constantly, complained of nausea, and vomited a small quantity of partially digested food. The height of the primary fever was reached at 3 p. m., February 10, *i. e.*, 22 hours after the commencement of the attack, when the temperature was 102.8° and the pulse 98. Remission of the fever to 99.4° and pulse to 74, occurred at 6 a. m., February 11, making the duration of the primary paroxysm 36 hours. Twenty-four hours after the remission had occurred, the temperature had risen to 102.4° with a pulse of 70. The fever continued to steadily increase until midnight of February 12, when a temperature of 105° F. was recorded, with a pulse of 90. The subsequent course was that of a case of severe yellow fever. Slight oozing of blood

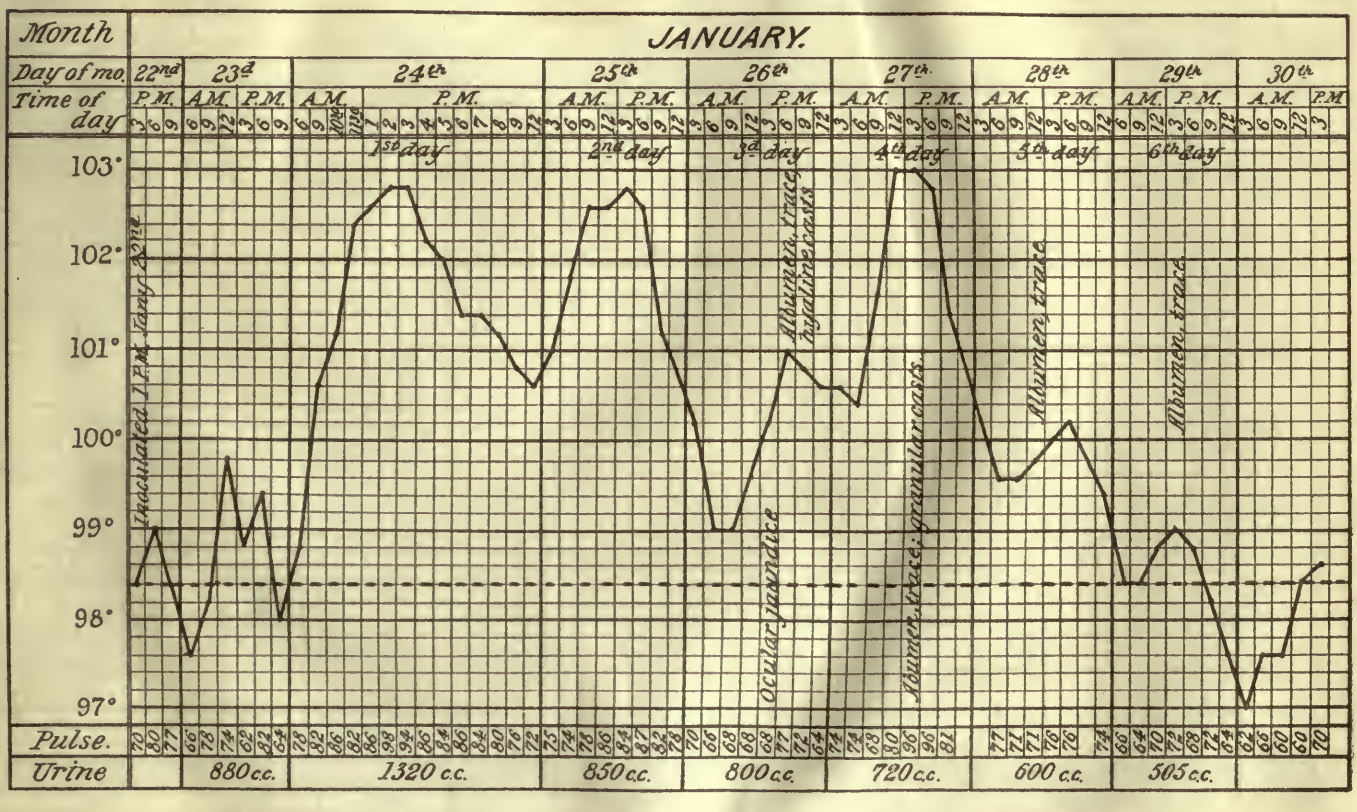

Chart III.—Yellow fever produced by injection of .5 cc. of blood. Period of incubation, 3 days, 1 hour.

from the gums occurred as early as the third day. Ocular jaundice, beginning on the third day, became later very distinct and was associated with general jaundice. Albumin, however, did not appear until the sixth day. The fever subsided on the ninth day, and was followed by a slow convalescence. The subject had been in strict quarantine for a period of 78 days prior to inoculation. (Chart VII.)

CASE VIII.—C. S., American, nonimmune, aged 28, with his full consent, was bitten at 2 p. m., February 7, 1901, by 3 mosquitos that had been contaminated 16 days previously by biting a fatal case of yellow fever on the second day of the disease. The subject remained well until the early afternoon of the third day, February 10. He ate his dinner at noon with good appetite. At 1 p. m., his temperature was 100° F., pulse, 90. Frontal headache was now complained of. This became rapidly more marked, and pains in the limbs were also present. Three hours later, 4 p. m., the fever had risen only ½ of a degree, but at 6 p. m. it had reached 103° F. and pulse, 96. At this hour he had severe headache and backache, with general pains over the body. The facial expression was now characteristic. Eyes brightly injected, photophobia well marked, and face decidedly congested. At 9. p. m. temperature was 103.2° and pulse 112. The skin was moist. Remission occurred at 6 a. m., February 12, 41 hours after the commencement of the febrile paroxysm. The secondary fever, which was moderate in character, lasted 4 days, the fever subsiding on the seventh day. Ocular jaundice was slight. A few hyaline casts were present on the third and subsequent days, but no albumin was found until 1 p. m., February 18, that is, 36 hours after the fever had subsided. It was present as a distinct trace in all specimens examined until 3 p. m., February 23. Convalescence was rapid. The subject had been in quarantine for a period of 25 days prior to inoculation. (Chart VIII.)

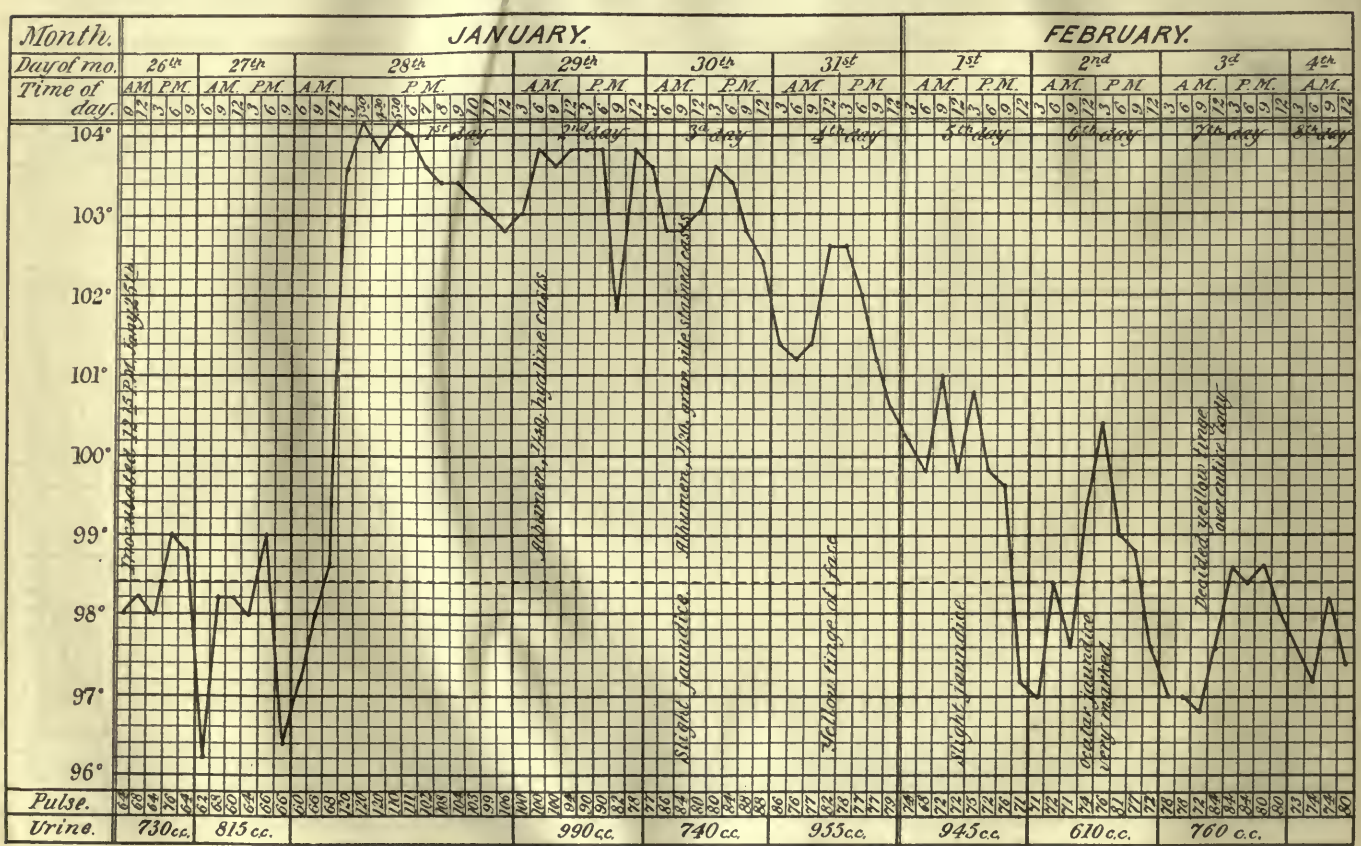

Chart IV.—Yellow fever produced by injection of 1 cc. of blood. Period of incubation, 1 day, 19 hours.

The foregoing cases of experimental yellow fever (Cases V, VI and VII) are, we think, of especial importance as showing the length of time during which the mosquito may remain capable of conveying the infection. In previous papers we have reported 6 cases of yellow fever produced by the bites of mosquitos at intervals varying from 12 to 24 days after the contamination of the insects. In the cases here reported the periods intervening between the contamination of the insect and the production of the disease were much longer, viz.: 39, 51 and 57 days, respectively. As one of these insects lived until the sixty-ninth and the other until the seventy-first day after contamination, we have for the first time an explanation of the fact, several times noted in the literature, that the contagion of yellow fever may cling for several months to a building that has been vacated by its occupants, or to the infected area of a town, even though this latter has been entirely depopulated. These particular insects, also, were contaminated at a later stage of the disease than in any of our other cases, *i. e.*, on the third day and during the secondary rise of the fever, following a complete intermission in the temperature. We have, therefore, been able to demonstrate that the parasite is present in the general circulation both after and before the stage of remission. How much later in the disease the parasite may still be found—a matter of much interest and importance—the observations thus far made do not determine. Although the 3 mosquitos applied on the third day—as above stated—acquired the parasites and were able to affect 3 individuals with yellow fever, a single mosquito applied to the same case of yellow fever on the fourth day of the disease failed to obtain the parasite, as shown by the negative result following its bite 40 days after contamination. That not all mosquitos become infected, however, with the parasite by biting yellow fever patients is shown by several observations made by us. We submit only one.

CASE IX.—J. W., American, nonimmune, was with his full consent, on January 25, 1901, bitten by 12 mosquitos—C. fasciatus—that had fed on a case of mild yellow fever—Martinez by name—on January 3, 1901, within 8 hours of the commencement of the attack. Although these mosquitos had been kept at a summer temperature for 22 days the result of the experiment was entirely negative. That the parasites were present in Martinez's blood at the end of 24 hours was fully shown by the effect produced by injecting 2 cc. of his blood drawn at this time beneath the skin of Case I of this report.

Observations such as the foregoing would indicate

that the mosquito at certain periods of the disease may fail to obtain the parasite, owing to its absence at that particular time from the capillary circulation. Concerning the matter of the propagation of yellow fever by other species of Culex than C. fasciatus, we have only 1 negative observation to record of an individual bitten by 5 C. pungens that had been contaminated by biting a case of yellow fever 19 days previously. To a single negative experiment such as this no importance can be given. So that this question must be left for future observations to determine.

Touching the subject of the possible transmission of the parasite to the daughter insect by means of infection of the ovum, we have also but a single observation to record. In this case the bites of 14 mosquitos hatched from the ova of a mosquito—C. fasciatus—that had already shown itself capable of conveying the disease—were followed by an entirely negative result.

Including the cases heretofore reported by us, we have thus far succeeded in conveying yellow fever to 12 individuals by means of the bites of contaminated mosquitos, and to 4 other persons by subcutaneous injection of blood taken from cases of this disease—a total of 16 cases. While ordinarily so small a number of cases would not be sufficient to enable one to arrive at definite conclusions concerning the general character and course of an acute infectious disease, the conditions under which the majority of these cases were observed were such as to give us valuable data concerning two matters of very great practical importance in connection with this disease, viz., the period of its incubation and the difference in degree in the character of its attacks. Further, as these cases were kept under constant observation, even from the time of inoculation, we are not only able to report upon the earliest premonitory symptoms, but also to give the primary temperature curve; and, in addition, to note the time of appearance of albumin in the urine, all of which are of interest in the clinical history of yellow fever.

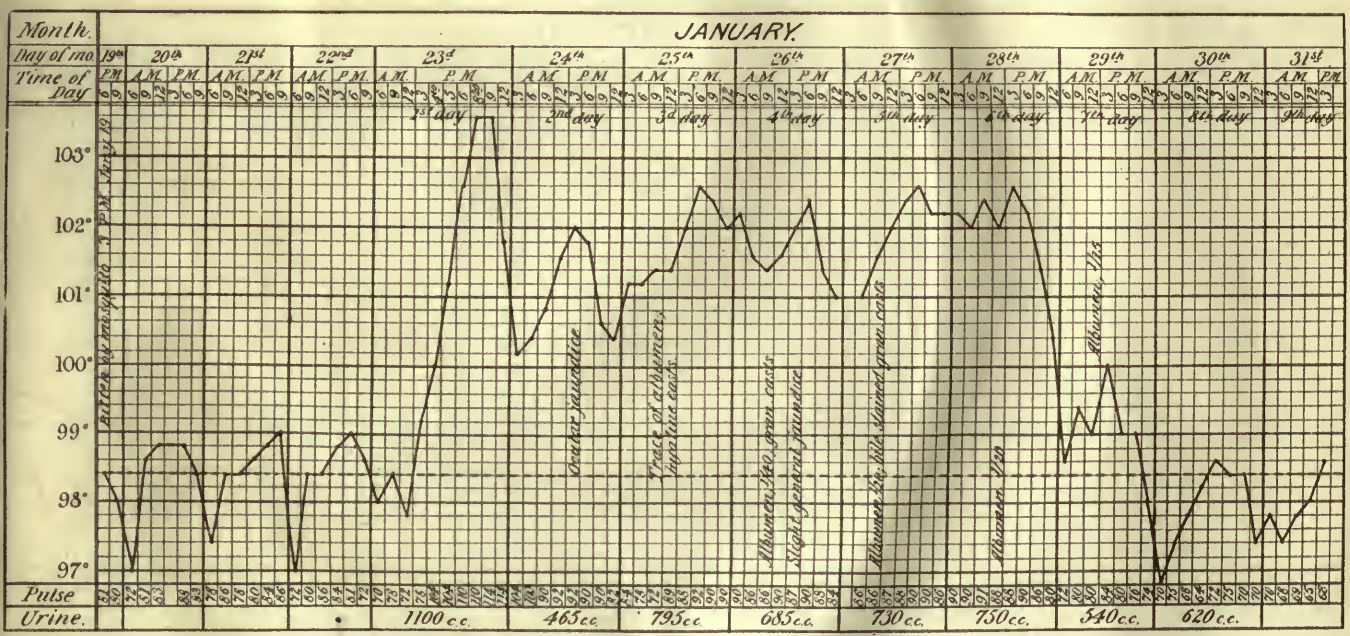

Chart V.—Yellow fever produced by the bite of Culex fasciatus. Period of incubation, 3 days, 23½ hours.

Period of Incubation.—The accurate determination of the period of incubation of any one of the acute infectious diseases is always a matter of scientific interest. If the disease is one which, like yellow fever, is of exotic origin and whose importation is liable to give rise to a widespread epidemic, then the determination of its incubative stages becomes of the highest practical importance. This importance, as a question of public hygiene, is increased, if as recent observations would seem to indicate, the importation of this disease is brought about only by the sick individual and not by his baggage or clothing. While the older authors were willing to prolong the period of incubation of yellow fever to 2 or 3 weeks or even longer, the tendency of physicians at the present time, is to shorten this stage to about 5 days. Reference to a few of the later textbooks on the Practice of Medicine will sufficiently indicate this. Davidson in Allbutt's System,[1] puts down the period of incubation as "ranging between 24 hours and 4 or 5 days." Stevens[2] says that it may vary from "a few hours to a week." Osler[3] says that the "period of incubation is usually 3 or 4 days, but it may be less than 24 hours or prolonged to 7 days." According to Tyson,[4] "yellow fever has a period of incubation of from 24 hours to 5 days, very rarely exceeding the latter." Sternberg[5] says that this period "does not usually exceed 4 or 5 days and may be less than 24 hours." Carter[6] in a recent valuable paper, gives the results of his studies on the period of incubation of yellow fever, based on observations extending over a considerable number of years. Under Class III of his observations, which are the most valuable, he includes "those persons, who, living in a clean environment, go into an infected one, stay only a short time, and then return to a clean environment where they remain until the fever develops." Of 12 cases thus accurately observed by himself the incubative stage was as follows:

2	cases with	3	days incubation.
6	"	" 3+	" "
2	"	" 4	" "
1	case	" 4½	" "
1	"	" 5¾	" "
12			

The following table gives the result of our observations in 16 cases of experimental yellow fever.

[1] A System of Medicine, London, 1897, Vol. II, p. 391.
[2] Practice of Medicine, Philadelphia, 1898, p 286.
[3] The Practice of Medicine, New York, 1899, p. 185.
[4] Practice of Medicine, Philadelphia, 1900, p. 85.
[5] Buck's Reference Handbook of the Medical Sciences, 1889, Vol. viii, p. 58.
[6] The Period of Incubation of Yellow Fever, New York Medical Record, March 9, 1901.

TABLE I.

Period of incubation of experimental yellow fever:

No. of case.	Date of inoculation	Method of Inoculation.	Date of commencement of attack.	Incubation.
1	2 p.m., Aug 27, 1900	Mosquito	9 a.m., Aug. 31, 1900	3 dys. 7 hrs.
2	11 a.m. " 31 "	"	1 p.m., Sept. 6, "	6 " 2 "
3	2 p.m., Dec. 5, "	"	11 30 p.m., Dec. 8, "	3 " 9½ "
4	1 p.m., " 8, "	"	9 a.m., " 14, "	5 " 17 "
5	10.30 a m., Dec. 9, "	"	9.30 p.m., " 12, "	3 " 11½ "
6	4.30 p.m., " 11, "	"	12 noon, " 15, "	3 " 19½ "
7	12 noon, " 21, "	"	11 a.m., " 25, "	3 " 23 "
8	11 a.m., " 30, "	"	10 30 a.m., Jan. 3, 1901	3 " 22½ "
9	11 a.m., Jan. 4, 1901	Blood inject.	9 a.m., " 8, "	3 " 22 "
10	9 p.m., " 8, "	" "	9 a.m., " 11, "	2 " 12 "
11	3.30 p.m, " 19, "	Mosquito	3 p m., " 23, "	3 " 23½ "
12	1 p.m., " 22, "	Blood inject	9 a.m., " 24, "	1 " 19 "
13	12.15 p m., " 25, "	" "	1.15 p.m., " 28, "	3 " 1 "
14	9 30 a.m., " 31, "	Mosquito	12 noon, Feb. 3, "	3 " 2½ "
15	11 a m., Feb. 6, "	"	5 p.m., " 9, "	3 " 6 "
16	2 p.m., " 7, "	"	12 noon, " 10, "	2 " 22 "

The average period of incubation of the 16 cases embraced in Table I will be found to be 87¼ hours, or 3 days 15¼ hours. If we separate the 12 mosquito infections from the 4 cases produced by the injection of blood, we have for the former a period of incubation of 94 hours or 3 days and 22 hours, and for the latter, an incubative stage of 67½ hours, or 2 days, 19½ hours. The average period of incubation, therefore, in the cases brought about by subcutaneous injection of blood was shorter by 26½ hours than those occasioned by the mosquito's bite. By the former method, this stage varied from 43 hours to 94 hours, while in the mosquito infections the shortest incubative period was 70 and the longest 146 hours. If we accept those cases produced by the mosquito's bite as the usual method of propagation of this disease, it will be observed that of the 12 cases 1 occurred on the third day; 9 on the fourth day; 1 on the sixth day and 1 at the beginning of the seventh day after incubation.

While our results, therefore, confirm the statement of later writers that the period of incubation of yellow fever does not usually exceed 4 or 5 days, they also seem to indicate very plainly that this stage may be prolonged more frequently, perhaps, than had been supposed.

In 16.6% of our cases, the period of incubation exceeded the usual quarantine period of 5 days. If we add Carter's cases to those observed by us, we find that of 24 cases, the period of incubation exceeded 5 days in 3, or 12.5%. We will not further dwell on this subject than to remark that cases No. 2 and No. 4 of our series, could have passed quarantine on the morning of the sixth day after inoculation, with a clinical thermometer under the tongne, without exciting any suspicion by reason of the presence of fever.

Character of the Attack.—We desire to call attention particularly to the difference in the degree of severity of the attack as shown by our experimental cases. Like all of the other acute infectious diseases, we have reason to expect that yellow fever will affect different individuals according to their individual susceptibilities, and hence that we will encounter mild as well as severe cases. The results which we have obtained confirm this expectation. Based upon the character of the attack, the 12 cases due to mosquito inoculation may be divided as follows:

Severe	2
Moderately severe	6
Mild	3
Very mild	1
	12

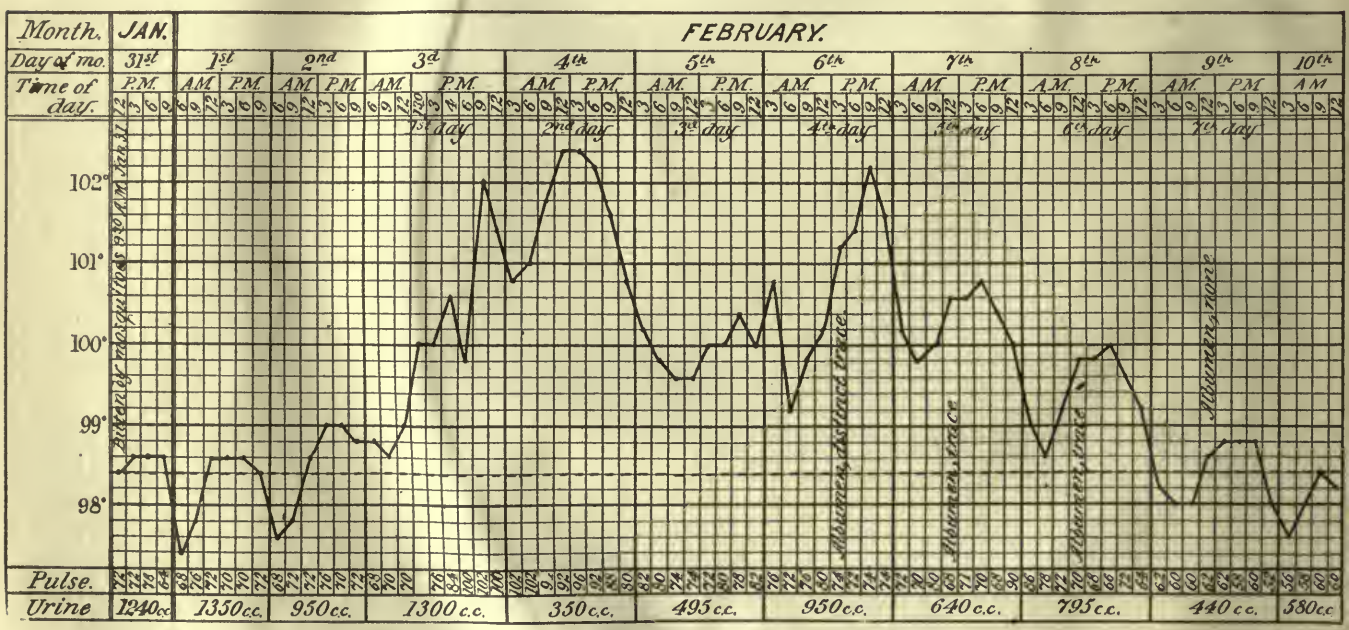
Month. JAN. FEBRUARY.
Day of mo. 31st 1st 2nd 3d 4th 5th 6th 7th 8th 9th 10th
Time of day. P.M. A.M. P.M.
1st day 2nd day 3d day 4th day 5th day 6th day 7th day
102°
101°
100°
99°
98°
Pulse.
Urine
1240cc 1350c.c. 950c.c. 1300c.c. 350c.c. 495c.c. 950c.c. 640c.c. 795c.c. 440c.c. 580cc

Chart VI.—Yellow fever produced by bite of Culex fasciatus. Period of incubation, 3 days, 2½ hours.

The 4 cases produced by the injection of blood gave the following result:

Severe	1
Moderately severe	2
Mild	1
	4

Thus the cases which were mild or very mild in character constituted 33% of those infected by the mosquito's bite, and 25% of those produced by blood injection. It is to the diagnosis of the former cases that we desire to direct special attention. To one familiar with yellow fever, or even to one unfamiliar with its clinical features, the diagnosis of our severe and moderately severe cases should have presented no difficulty. The sharp headache and backache, the characteristic facies, the ocular jaundice, together with the presence of albumin in the urine, except in 1 case to be hereafter referred to, with the negative result of a blood examination, would have been a sufficient complex of symptoms to have rendered the diagnosis tolerably certain. Even in our 3 "mild" cases, were the physician on his guard and acquainted with the temperature curve and pulse from

the very onset of the attack, and besides careful in the testing of each specimen of urine passed, a diagnosis of yellow fever could have been made with reasonable probability. We believe, however, that in the ordinary course of events, where there was no reason to suspect the presence of yellow fever, the average practitioner would have probably failed to appreciate the true nature of these attacks. Such was the admission which we, ourselves, were compelled to make, although in constant attendance and thoroughly acquainted with these cases from their very beginning. The short duration of the primary fever, in one instance, the rapid amelioration of the earlier symptoms in all, the absence of albumin during the first 3 days or its presence, as a mere trace, in certain specimens, followed by its absence in succeeding specimens; the slight icteroid hue of the conjunctiva—to be obtained only in a certain light and then doubtfully—all served to render a positive diagnosis exceedingly difficult. Several physicians, who saw these milder cases, at our request, readily acknowledged the improbability of a correct diagnosis being made, in the absence of the complete data which

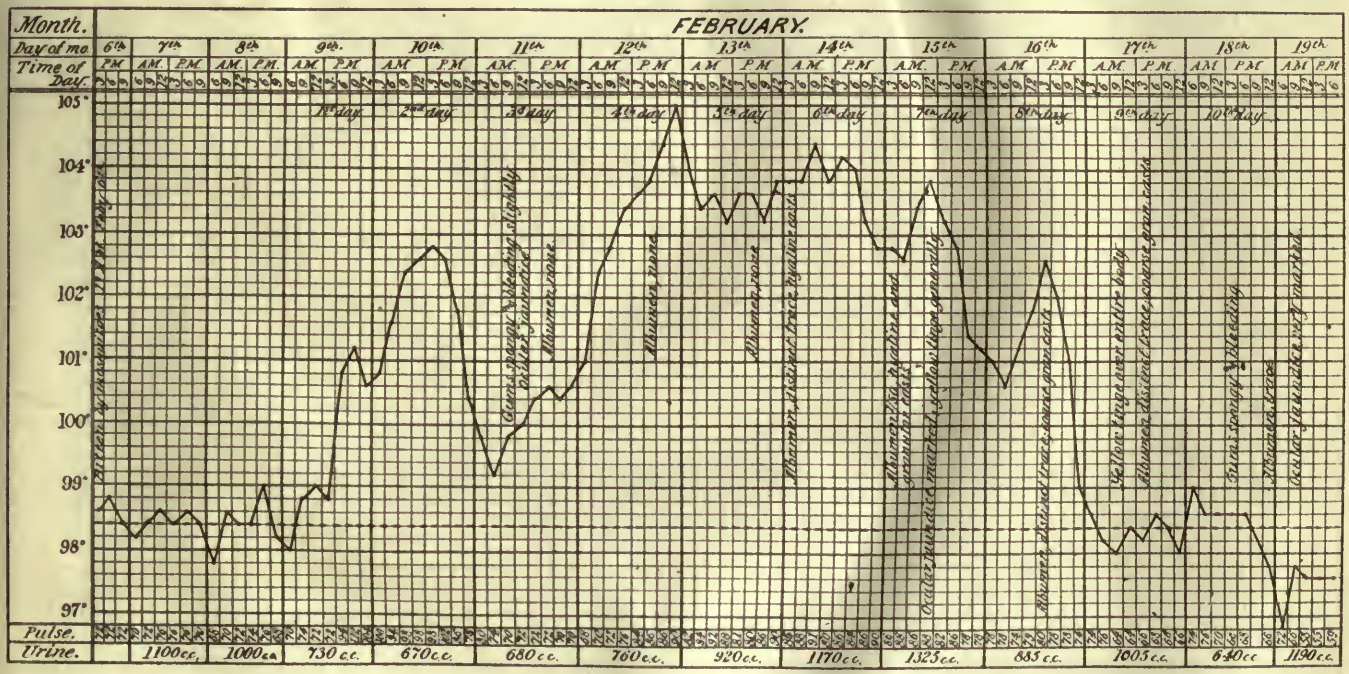

Chart VII.—Yellow fever produced by bite of Culex fasciatus. Period of incubation, 3 days, 6 hours.

we were able to furnish concerning them. In the one case which we have classed as "very mild" yellow fever, we believe that the matter of a correct diagnosis would have been in the highest degree improbable. The attack consisted of a single paroxysm of 33 hours duration, during which the temperature only reached 101° for a period of 6 hours. It is true that albumin was found in the urine at the end of 37 hours, but the quantity was exceedingly small and only to be detected by the most delicate testing. It was only present in 1 of 2 specimens passed on the third day. A slight trace was present in a specimen passed at 9 a. m. of the fourth day and in that passed at 4.40 p. m. of the fifth day. Intervening specimens of urine, several in number, contained no albumin. A well-marked papular eruption which appeared on the fourth day of the disease, and which was confined to the trunk and arms, would hardly have rendered the diagnosis easier. We suppose that during the prevalence of an epidemic of yellow fever, a physician who was thoroughly acquainted with the several types of this disease, would probably class this case as one of extremely mild yellow fever, with a wide margin for doubt. Under all other circumstances, we feel confident that cases of this character would escape diagnosis. That cases of mild yellow fever may and do serve as foci for the development of other cases, our own observations demonstrate, since we have been able to propagate the disease from one such mild case by means of the bites of contaminated mosquitos, and from another case of like character by the subcutaneous injection of 2 cc. of blood.

THE ONSET AND PREMONITORY SYMPTOMS.

Of the 12 cases produced by mosquito inoculation, the onset was sudden in 2 and gradual in 10. In both of the former the attack occurred during the night, the patient, also, in both instances, being awakened by the occurrence of a decided chill. In 1 of the 2 cases of sudden onset, the subject complained of slight supraorbital headache during the afternoon preceding the attack. Of 4 cases produced by the injection of blood, the onset was sudden in 1—the only case marked by a chill—and gradual in 3. The attack in all of these blood cases began during the daytime. As writers generally state that in yellow fever the chances of infection are greater during the night, we have thought that, perhaps, the time of inoculation of our experimental cases (which was during the day except in 1 instance), might have had some influence upon their occurrence, as a rule, during the daytime. If the hour of inoculation in all of our cases should have taken place at about sunset, then, with the same period of incubation, 7, or 43%, would have experienced their attacks at night.

Of the 13 cases in which the onset was gradual—by mosquito inoculation, 10; by blood injection, 3—*frontal headache*, the pain being referred to the supraorbital region and extending into the temporal region, was the most frequent premonitory symptom. It was present in 10 and absent in 3 cases. This symptom preceded the attack in these cases at intervals varying from 2 to 48 hours. In 2 cases no premonitory headache was complained of, while in 1 case *occipital* headache preceded the onset by 24 hours, and continued to be of this character throughout the attack. *Dizziness* was complained of by 3 of the gradually developing mosquito cases, and a sense of weight in the lower extremities by the 2 others

belonging to this group. All of the cases of gradual onset (13 in number) complained of lassitude and want of appetite, on which account all took to their beds prior to the onset of fever. Ten of these individuals complained of slight sensations of chilliness—generally confined to the lower extremities—at the beginning of the attack, while in 3 this symptom was entirely absent. In our experimental cases, therefore, *frontal headache* and *muscular debility* were the most frequent and prominent premonitory symptoms. After the attack had developed, the symptoms corresponded to those described at length by various writers and with which all are familiar, except that black vomit did not occur in any of our cases.

THE FEVER.

As we have had prepared charts of our several cases of experimental yellow fever, from which all the data concerning temperature and pulse can be obtained, it will not be necessary for us to make extended remarks under this heading. Medication being practically nil in our cases, both temperature curve and pulse can be accepted as faithfully representing what normally takes place in an attack of this disease. Where icewater enemas or cold sponge-baths were used by the attending physician, this is noted on the chart. It should also be remembered that our patients were put to bed at the very first manifestation of the disease, and carefully transported to the yellow fever wards on the very same beds which they had occupied in camp. This probably had some effect upon the subsequent course of the fever. The record of temperature being taken every 3 hours from the time of inoculation enables us to give the complete curves of both the primary and secondary febrile paroxysm. Our charts therefore differ considerably from those given by the various writers on yellow fever in that they round out, as it were, the primary stage more fully. An examination of these charts will show that although the primary rise of temperature is tolerably abrupt and reaches its height within a comparatively short time, it does not reach its maximum so quickly as the description of writers would seem to indicate. The tri-hourly record in 10 of our mosquito inoculations shows that this period of primary rise varies from 12 to 24 hours. In 3 cases it was 12 hours; in 2, 15 hours; in 1, 15½ hours; in 1, 20½ hours; in 1, 22½ hours, and in 2, 24 hours. The average period for the 10 cases was therefore a fraction over 16 hours.

In striking contrast to these was the short period of the primary rise of temperature in the 4 cases produced by blood injection. In these it varied from 2½ to 9 hours, the remaining 2 cases giving 6 and 7 hours respectively, the average for the 4 cases being only 6 hours. In all of the 12 cases due to mosquito inoculation, the primary rise of temperature was followed by a distinct remission or intermission which was generally reached within 48 hours. The same remission was present in 3 of the 4 cases produced by blood injection. We

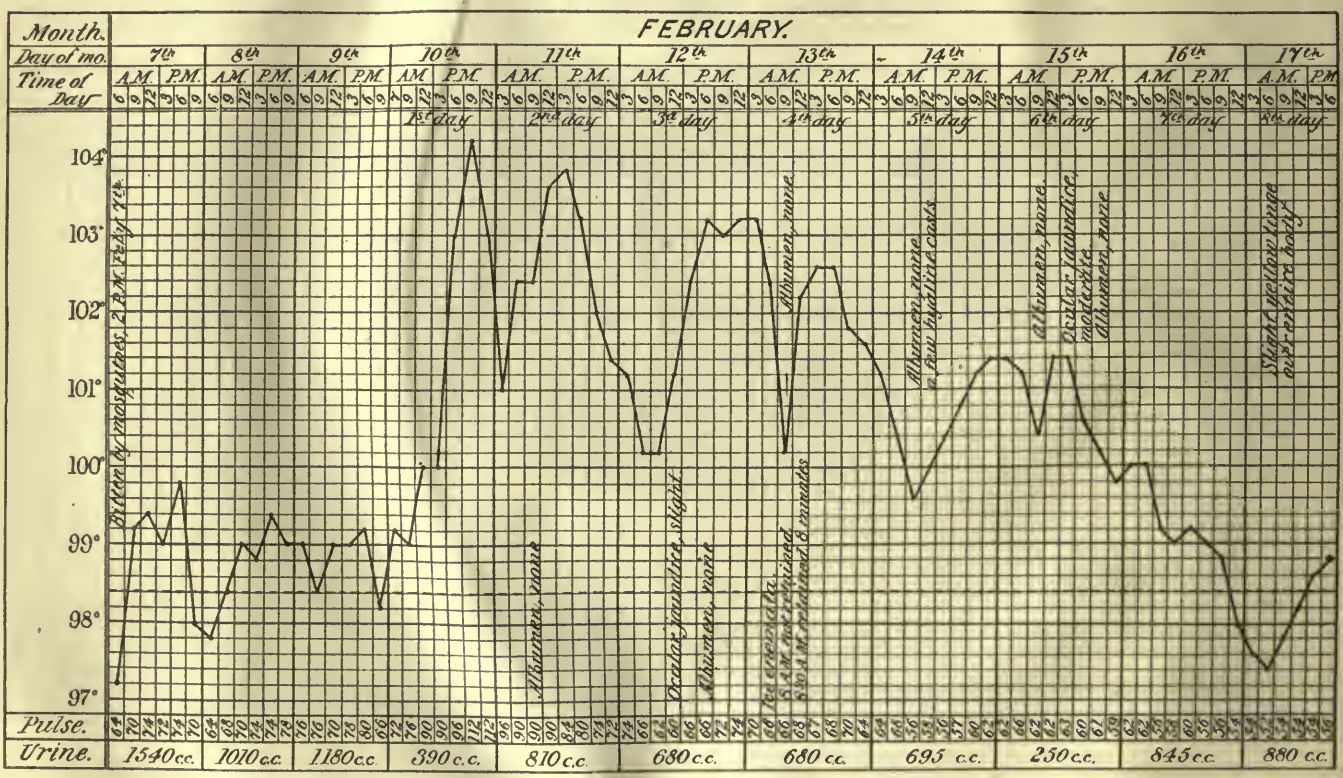

Chart VIII.—Yellow fever produced by bite of Culex fasciatus. Period of incubation, 2 days, 22 hours.

are able to give the duration of the primary paroxysm accurately in the 10 cases produced at Camp Lazear by the bites of mosquitos, viz.:

1	case	33 hours.
1	"	33½ "
1	"	36 "
1	"	39 "
1	"	41 "
3	"	45 "
1	"	52 "
1	"	60 "
Total 10		

The average duration of these 10 cases was 43 hours. In the 3 cases caused by the injection of blood the length of the primary paroxysm was 24 hours in 2 cases and 36 hours in 1 case—the average being 28 hours. We may therefore say that not only the average period of incubation, but also the primary rise of temperature, as well as the length of the first febrile stage were all shorter in the cases produced by blood injection than in those due

to the mosquito's bite. Of the 12 cases due to the latter mode of inoculation the first febrile stage was followed by an intermission in 2, and a remission in 10 cases. Of those produced by the injection of blood, 3 showed a distinct remission and 1 no intervening fall of temperature. The duration of this intermission varied from 3 to 27 hours. This was followed by a second febrile stage or paroxysm in 11 of the 12 mosquito inoculations, and in 3 of the 4 cases due to the injection of blood. The duration of this second febrile paroxysm was from 2 to 5 days.

Experimental yellow fever then, as we saw it at Camp Lazear, consisted of a primary and secondary febrile paroxysm, with an intervening remission or intermission—more frequently the former. The secondary was much longer than the primary febrile stage.

In 1 of our mosquito inoculations a relapse occurred on the ninth day of the disease, and was characterized also by 2 febrile stages with an intervening remission. There were present headache and backache, with injection of the eyes and face, together with hemorrhage from the gums, as had been observed in the primary attack.

The want of correlation between temperature and pulse (Faget's law), upon which clinicians rely as an important diagnostic sign, was seen as a rule in our experimental cases, *i. e.*, after the passage of the first febrile stage. In 1 case produced by the injection of blood, Faget's law was not complied with.

The Urine.—We have confined our examination of the urine largely to testing for the presence of albumin and to the ordinary microscopic examination of this fluid. Heat and nitric acid was the method used in all cases for the detection of albumin, the specimen having first been carefully filtered.

Under this heading we desire to speak only concerning the presence of albumin. All writers dwell on the importance of a careful examination of the urine in suspicious cases of fever, since the presence of albumin in the urine is such a constant sign in yellow fever. Guiteras, who has had a large experience with this disease, says: "The albumin appears in the urine usually on the third or fourth day of the disease. It may be very transient. In many mild cases the albumin is present only in the urine passed in the evening of the third or fourth day. In many cases it is only a trace." We may say that the results obtained from examination of the urine of experimental yellow fever accords for the most part with the statements above quoted.

TABLE II.

Case.		Albumin during period of incubation.	Time of appearance of albumin during the attack.	Time of disappearance of albumin dating from appearance.	Maximum quantity.	Remarks.
1	Mosquito-inoculation.	None.	42 hours.	10th day.	8/10 by vol.	
2		"	25 "	11th "	3/10 " "	
3		"	82½ "	15th "	2/10 " "	
4		"	48 "	5th "	Distinct trace.	
5		"	64½ "	4th "	Light "	
6		"	43½ "	3rd "	Distinct trace.	
7		"	37½ "	8th "	" "	
8		"	43 "	9th "	1/40 by vol.	
9		"	42 "	12th "	1/20 " "	
10		"	75 "	8th "	Distinct trace.	
11		"	105 "	15th "	1/40 by vol.	
12		"	None		1/20 " "	Albumin did not appear till 36 hours after fever had subsided and persisted for 5 days.
13	Blood-inoculation.	None.	61 hours.	13th day.	Distinct trace.	
14		"	17 "	12th "	" "	
15		"	57 "	9th "	" "	
16		"	18½ "	15th "	1/10 by vol.	

In our earlier cases we did not examine for albumin until the onset of the attack. In our last 8 cases (those embraced in this report) we examined daily specimens from the time of inoculation until the attack began, and thereafter we endeavored to examine every specimen passed by the patient. Table II gives the results obtained.

An examination of the cases presented in this table will show that of the 12 mosquito inoculations, the earliest appearance of albumin was at the beginning of the second day in 1 case; during the second day in 5; at the end of the second day in 1; during the third day in 1; during the fourth day in 2; during the fifth day in 1; while in 1—a well-marked case—no albumin could be detected till 36 hours after the temperature had reached the normal, *i. e.*, till the second day of convalescence; it then persisted during 5 days. In all 23 specimens of urine were examined in this case during the 6 days of fever, but with an entirely negative result as regards the presence of albumin. An occasional hyaline or fine granular cast could be found in the majority of these specimens. We submit this case of experimental yellow fever as one of especial importance from the clinical standpoint, since the absence of albumin, during the attack would have probably led to an error in diagnosis. How very exceptional such cases may be, we have no means of knowing.[1]

It will be observed that the quantity of albumin present in this series of cases was very moderate, except in Cases I and II of Table II. These cases were the only 2 of the 16 that were not placed in bed from the very beginning of the attack. In the remaining 14, all of whom were kept at absolute rest during the whole period of the fever, the amount of albumin was small in 6 and insignificant in 8. We are inclined to believe, therefore, that both the course of the fever, as well as the quantity of albumin, were favorably affected by the early enforced rest of our patients.

In conclusion we desire to invite attention to 2 matters which we consider of considerable importance in connection with the possible importation and propagation of yellow fever. First, we believe that the facts herewith presented indicate that the period of incubation of yellow fever occasionally exceeds the quarantine period of 5 days, and that although exceptional, this must not be left out of consideration. Secondly, that our observations emphasize anew the importance of the recognition by the profession of mild and very mild cases of yellow fever. Guiteras[2] says: "I cannot insist too much upon the importance of the diagnosis of the first case of yellow fever in a locality." He adds: "Undoubtedly the cause of the epidemic of yellow fever is to be found in the introduction into a community of cases that are not suspected to be yellow fever." In the light of our investigations, we feel constrained to remark that the failure to detect cases of mild yellow fever, has been, we believe, the most important factor in the development of the theory of the propagation of this disease by fomites.

[1] It is of interest to note that this particular individual, 2 weeks prior to successful inoculation and while in quarantine, had an intermittent albuminuria which lasted 3 days.

[2] Report of United States Marine Hospital Service, Vol. 27, 1897-1898, p. 300.

Tuberculin.—Professor Robert Koch publishes in the *German Medical Weekly* a declaration that Dr. Goetsch, of the Slawentzitz Hospital, has used for 10 years past tuberculin against pure tuberculosis with unvarying success.

Memorial to Dr. Lazear.—On commencement day at Trinity Hall Military School, Washington, Pa., a tablet was unveiled to the memory of Dr. Jesse W. Lazear, of Baltimore, who sacrificed his life while investigating the causes of yellow fever in Cuba.

Long Island College Hospital.—George Foster Peabody and his brothers have agreed to contribute $50,000 for the building and furnishing of an operating room, as a memorial to the late Dr. A. J. C. Skene, for this institution, which is to be practically rebuilt.